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Signed P. Mahoney

Dated 16 August 2000

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GB9918965.6.

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

CEREBRUS PHARMACEUTICALS LIMITED,
Incorporated in the United Kingdom,
Oakdene Court,
613 Reading Road,
Winnersh,
WOKINGHAM,
RG41 5UA,
United Kingdom

[ADP No. 07745409001]

Patents Form 1/77

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THE PATENT OFFICE 11 AUG 1999

Request for grant of a patent

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12AUG99 E468970-2 D00019
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1/77

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1. Your reference — **P022523GB**

2. Patent application number *(The Patent Office will fill in this part)* — **9918965.6** — **11 AUG 1999**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CEREBRUS LIMITED
OAKDENE COURT
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SECTION 130(7) (1977 ACT) APPLICATION FILED 27-8-99

Patents ADP number *(if you know it)* 7035181002

If the applicant is a corporate body, give the country/state of its incorporation — **UNITED KINGDOM**

4. Title of the invention — **CHEMICAL COMPOUNDS XXI**

5. Name of your agent *(if you have one)* — **Carpmaels & Ransford**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
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WC1A 2RA

Patents ADP number *(if you know it)* — **83001**

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application.

Signature Date

Carpmaels & Ransford **11th August 1999**

12. Name and daytime telephone number of person to contact in the United Kingdom **PAUL N. HOWARD** **0171 242 8692**

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CHEMICAL COMPOUNDS XXI

The present invention relates to indoline derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, *"Obesity: Trends and Treatments"*, *Scrip Reports*, *PJB Publications Ltd*, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2, and obesity as a BMI greater than 30 kg/m^2. There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

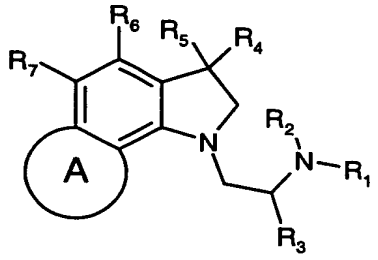
blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin®) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, **98**, 93-100; G.A. Kennet, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, **141**, 429-453) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, **113**, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single injection of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, **116**, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, **113**, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, **374**, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, **36**, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders. WO 9517405 discloses methods for the preparation of indolines for use as melatonin receptor ligands.

It is an object of this invention to provide selective, directly acting $5HT_2$ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for $5\text{-}HT_{2B}$ and/or $5\text{-}HT_{2C}$ receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting $5\text{-}HT_{2C}$ receptor ligands, preferably $5\text{-}HT_{2C}$ receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided a chemical compound of formula (I):



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4 and R_5 are selected from hydrogen and alkyl;

R_6 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl;

A is an optionally substituted 5 or 6-membered unsaturated or saturated ring optionally containing one or more substituted or unsubstituted heteroatoms.

Compounds of the present invention include salts and addition compounds of the compounds of formula (I). The present invention also includes prodrugs which are metabolised in vivo to a compound of formula (I).

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5, C_6 or C_7. Where acyclic, the alkyl group is preferably C_1 to C_{10}, more preferably C_1 to C_6, more preferably methyl, ethyl, propyl or butyl, more preferably methyl.

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteratom, such as pyridyl, pyrrolyl, furanyl and thiophenyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon containing groups such as

- alkyl,
- aryl,
- arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

- haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

- alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
- ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),
- aldehydes (e.g. carboxaldehyde),

ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl)

acids (e.g. carboxy, carboxyalkyl),

acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkycarbonylyoxy, alkycarbonylyoxyalkyl)

and amides (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

and carbamates (eg. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or dialkylaminocarbonyloxy, arylaminocarbonyloxy),

and ureas (eg. mono- or dialkylaminocarbonylamino or arylaminocarbonylamino);

nitrogen containing groups such as

amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl),

azides,

nitriles (e.g. cyano, cyanoalkyl),

nitro;

sulfur containing groups such as

thiols, thioethers, sulfoxides, and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl);

and heterocyclic groups containing one or more, preferably one, heteroatom,

(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2. Preferably, R_1 and R_2 are both hydrogen.

The compounds of formula (I) are selected from compounds in which R_3 is alkyl, preferably methyl.

R_4 and R_5 are selected from hydrogen and alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl. Preferably R_4 and R_5 are hydrogen or loweralkyl.

R_6 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl.

According to a further aspect of the invention, there is provided a compound of formula (I) for use in therapy.

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_2 receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment

(including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of obesity.

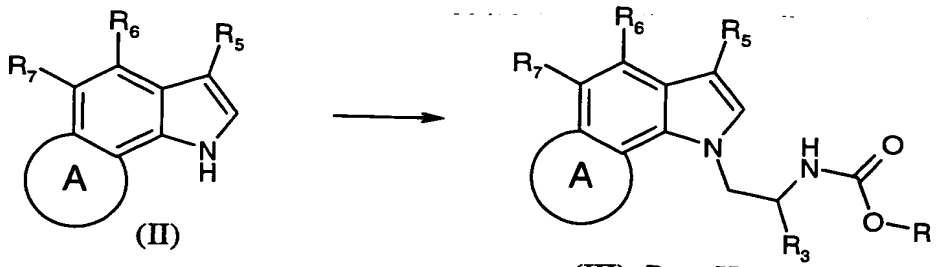
According to a further aspect of the invention, there is provided a method of treating a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

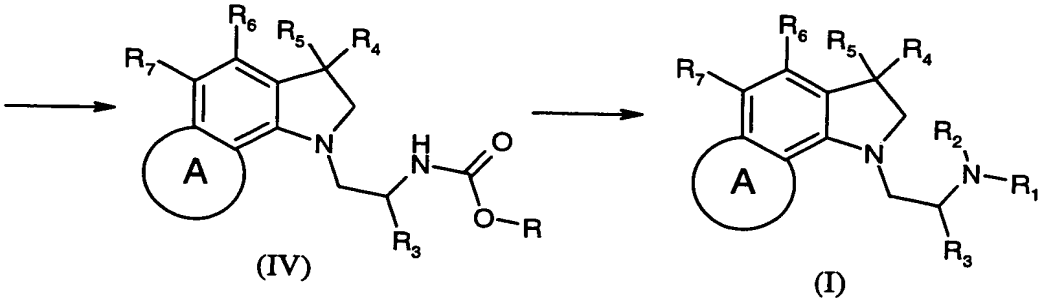
According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of preparing a compound of formula (I) described below in Reaction Scheme 1. R_1 to R_7 are as previously defined.

The N-alkylindole (III) may be formed by reaction of the indole (II) with an appropriate carbamylethylsulfonate in the presence of a strong base such as potassium hydroxide in a solvent such as methyl sulfoxide. Where required, the N-alkylindole (IV) may be obtained from the N-alkylindole (III) by reaction with an acylating agent eg. acetic anhydride in the presence of an acid catalyst followed by treatment with a reducing agent eg. diborane in a solvent such as THF. The indoline (V) may be obtained via reduction of the N-alkylindole (IV) with a reducing agent such as sodium cyanoborohydride or tetrabutylammonium borohydride in a solvent such as acetic acid or dichloromethane. The indoline (I) ($R_1 = R_2 = H$) may be obtained by reaction of the indoline (V) with a reagent suitable to reveal the protected amine function.

Reaction Scheme 1





The compounds of formula (I) (R_1 and/or R_2 = alkyl) may be prepared from compounds of formula (I) (R_1 = R_2 = H) by standard methods such as reductive alkylation with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

If, in any of the other processes mentioned herein, the substituent group R_4, R_5, R_6 or R_7 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4, R_5, R_6 or R_7 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds. Examples of acid addition salts are those formed

from inorganic and organic acids, such as sulfuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulfonic, p-toluenesulfonic, oxalic, hippuric or succinic acids.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions

may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilising and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula I to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2C} receptor the 5-HT_{2C} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for 5-HT_{2C} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, **118**, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [^{3}H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, **342**, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [^{125}I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, **9/10**, 3482-90.

The thus-determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	K_i (2C)	K_i (2B)	K_i (2A)
1	107	39	173
6	70	218	223

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR) in the following manner.

CHO cells expressing either the h5-HT_{2C}, h5-HT_{2A} or h5-HT_{2B} receptors were counted and plated into standard 96 well microtitre plates before the day of testing to give a confluent monolayer. The following day the cells were dye loaded with the calcium sensitive dye Fluo 3-AM by incubation with serum free culture maintenance media containing pluronic acid and Fluo 3-AM dissolved in DMSO at 37 °C in a CO_2 incubator at 95% humidity for approximately 90 minutes. Unincorporated dye was removed by washing with Hanks balanced salt solution containing 20mM HEPES and 2.5mM probenecid (the assay buffer) using an automated cell washer to leave a total volume of 100µl/well.

The drug (dissolved in 50µl of assay buffer) was added at a rate of 70µl/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements are taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10µM 5 -HT (defined as 100%) to which it is expressed as a percentage response (relative efficacy).Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

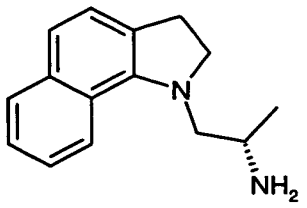
The thus determined activities of the Examples is shown in Table 2.

Table 2

Compound	h5-HT_{2A}		h5-HT_{2C}	
	EC_{50} (nM)	Relative Efficacy (%)	EC_{50} (nM)	Relative Efficacy (%)
1	1374	51	158	79
2	>10 000	-	1720	44
3	138	81	6	94
4	505	66	47	89
5	48	77	0.4	86
6	312	71	47	90
7	1835	14	440	68

Synthetic Examples

Example 1: (*S*)-1-(Benz[*g*]indolin-1-yl)-2-propylamine hemi-fumarate



(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-benz[*g*]indole

Benz[*g*]indole (1.5 g, 10 mmol) (Bartoli *et al.*, *Tetrahedron Lett.*, 1989, **30**(16), 2129-32) was added portionwise to a stirred suspension of powdered potassium hydroxide (85%, 4.8 g, 72 mmol) in methyl sulfoxide (50 mL). The mixture was warmed to 35 °C and stirred for 30 min. A solution of (*S*)-2-(*tert*-butoxycarbonylamino)propane methanesulfonate (11.4 g, 45 mmol) in methyl sulfoxide (20 mL) was added over 2 h. The mixture was stirred for 20 h and partitioned between water (100 mL) and ether (3 x 50 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (3:1)] to give the product (0.7 g, 12%) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 1686, 1529, 1366, 1176, 1058, 804 and 685; NMR δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 5.5 Hz), 1.54 (9H, s), 3.96-4.05 (1H, m), 4.36-4.51 (2H, m), 4.91 (1H, brs), 6.59 (1H, t, *J* 3 Hz), 7.04 (1H, d, *J* 3 Hz), 7.39 (1H, d, *J* 8 Hz), 7.48 (1H, d, *J* 8 Hz), 7.55 (1H, t, *J* 7 Hz) 7.66 (1H, d, *J* 8.5 Hz), 7.92 (1H, d, *J* 8.5 Hz) and 8.51 (1H, brs).

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-benz[*g*]indoline

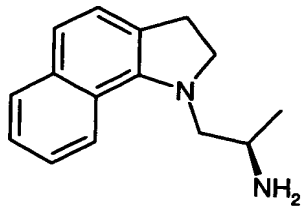
To a stirred solution of (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-benz[*g*]indole (0.49 g, 1.5 mmol) in acetic acid (10 mL) was added portionwise sodium cyanoborohydride (95%, 0.30 g, 4.5 mmol). The mixture was stirred for 16 h and partitioned between ether (40 mL) and saturated aqueous sodium bicarbonate solution

(3 x 50 mL). The organic layer was washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO_2; heptane-ethyl acetate (6:1)] to give the product (0.24 g, 49%) as a pale yellow solid: IR ν_{max} (Nujol)/cm^{-1} 1689, 1528, 1362, 1298, 1051 and 790; NMR δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.5 Hz), 1.45 (9H, s), 3.11-3.28 (2H, m), 3.32-3.42 (2H, m), 3.62-3.69 (2H, m), 3.98-4.08 (1H, m), 4.78 (1H, brs), 7.30-7.38 (1H, m), 7.33-7.41 (3H, m), 7.72-7.81 (1H, m) and 7.98-8.01 (1H, m).

(*S*)-1-(Benz[*g*]indolin-1-yl)-2-propylamine hemi-fumarate

To a stirred solution of (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-benz[*g*]indoline (0.23 g, 0.7 mmol) in dichloromethane (2 mL) was added dropwise trifluoroacetic acid (2 mL). The mixture was stirred for 1 h and partitioned between aqueous sodium hydroxide solution (2 M, 20 mL) and dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate) and concentrated *in vacuo* to give a pale yellow oil. The oil was dissolved in 2-propanol (5 mL) and the solution was heated to boiling then fumaric acid (0.08 g, 0.7 mmol) was added. The mixture was cooled to 0 °C and filtered. The filter-cake was dried *in vacuo* to give the product (0.13 g, 65%) as a white solid: mp. 205-207 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.23 (3H, d, *J* 6.5 Hz), 3.01-3.69 (7H, m), 6.39 (1H, s), 7.31-7.40 (4H, m), 7.83 (1H, m) and 8.06 (1H, m).

Example 2: (*R*)-1-(Benz[*g*]indolin-1-yl)-2-propylamine hemi-fumarate



(*R*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-benz[*g*]indole

(*R*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-benz[*g*]indole was prepared according to the method described in Example 1 using benz[*g*]indole and (*R*)-2-(*tert*-

butoxycarbonylamino)propane methanesulfonate to give the product (0.69 g, 35%) as a pale yellow solid: IR ν_{max} (Nujol)/cm^{-1} 1686, 1529, 1467, 1176, 1058, 804 and 722; NMR δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 7 Hz), 1.41 (9H, s), 4.16-4.28 (1H, m), 4.38-4.49 (2H, m), 4.91 (1H, brs), 6.59 (1H, d, *J* 3 Hz), 7.04 (1H, d, *J* 3 Hz), 7.40 (1H, t, *J* 7 Hz), 7.49 (1H, d, *J* 8.5 Hz), 7.55 (1H, t, *J* 7 Hz), 7.68 (1H, d, J 9 Hz), 7.91 (1H, d, J 8 hz) and 8.50 (1H, brs).

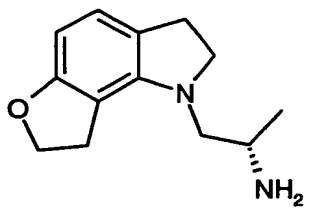
(*R*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-benz[*g*]indoline

(*R*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-benz[*g*]indoline was prepared according to the method described in Example 1 from (*R*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-benz[*g*]indole to give the product (0.14 g, 28%) as a pale yellow solid: IR ν_{max} (Nujol)/cm^{-1} 1689, 1528, 1362, 1298, 1169, 1051 and 789; NMR δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.5 Hz), 1.41 (9H, s), 3.07-3.23 (2H, m), 3.27-3.35 (2H, m), 3.56-3.62 (2H, m), 3.95-4.03 (1H, m), 4.72 (1H, brs), 7.21-7.24 (1H, m), 7.28-7.35 (3H, m), 7.72 (1H, d, *J* 7.5 Hz) and 7.93 (1H, d, *J* 7.5 Hz).

(*R*)-1-(6-(Benz[*g*]indolin-1-yl)-2-propylamine hemi-fumarate

(*R*)-1-(6-(Benz[*g*]indolin-1-yl)-2-propylamine hemi-fumarate was prepared according to the method described in Example 1 using (*R*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-benz[*g*]indoline to give the product (0.12 g, 95%) as a white solid: mp. 205-207 °C; NMR δ_H (400 MHz, DMSO-d_6) 1.24 (3H, d, *J* 6.5 Hz), 3.01-3.69 (7H, m), 6.39 (1H, s), 7.31-7.40 (4H, m), 7.83 (1H, m) and 8.06 (1H, m).

Example 3: (*S*)-1-(2,3,7,8-Tetrahydrofuro[*2,3-g*]indol-1-yl)-2-propylamine fumarate



2,3-Dihydrobenzo[*b*]furan-5-carboxaldehyde and 2,3-dihydrobenzo[*b*]furan-7-carboxaldehyde

To a stirred solution of 2,3-dihydrobenzo[*b*]furan (9.4 mL, 83.4 mmol) in dichloromethane (250 mL) under Ar at –5 °C was added dropwise titanium(IV) chloride (18 mL, 167.0 mmol) over 15 min, maintaining the temperature below 0 °C. After addition was complete, the red-brown reaction mixture was allowed to stir for a further 10 min before α,α-dichloromethyl methyl ether (8.3 mL, 91.6 mmol) was added dropwise [CAUTION – exotherm] maintaining the temperature below 0 °C. Upon complete addition, the vivid crimson reaction mixture was allowed to warm to ambient temperature over 2 h, and was then cautiously poured onto a saturated aqueous solution of sodium bicarbonate (700 mL). The mixture was filtered through a pad of Kieselguhr, which was washed through with dichloromethane. The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 400 mL). The combined organic fractions were washed with brine (300 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford a mixture [5-CHO : 7-CHO (4:1)] of aldehyde products (11.48 g, 93%) as a green-black liquid which was used without further purification.

Methyl 2-azido-3-(2,3-dihydrobenzo[*b*]furan-5-yl)propenate and methyl 2-azido-3-(2,3-dihydrobenzo[*b*]furan-7-yl)propenate

To a stirred solution of potassium *tert*-butoxide (31.0 g, 0.26 mol) in anhydrous methanol (220 mL) under Ar at –13 °C was added dropwise a mixture of methyl azidoacetate (31.7 g, 0.27 mol), and 2,3-dihydrobenzo[*b*]furan-5-carboxaldehyde and 2,3-dihydrobenzo[*b*]furan-7-carboxaldehyde (4:1 mixture; 10.15 g, 69 mmol) over 40 min. After complete addition, the reaction mixture was stirred at –10 °C for 1 h, then stored at 0 °C overnight (with a vent needle in place).

The reaction mixture was partitioned between ethyl acetate (750 mL) and water (1 L) and the aqueous phase was extracted with ethyl acetate (2 x 300 mL). The combined organic fractions were washed with brine (300 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford a crude oil. Purification by flash column chromatography [SiO_2; dichloromethane-heptane (1:1)] afforded a mixture [5-

substituted : 7-substituted (4:1)] of products (11.4 g, 68%) as a pale yellow solid which was used without further purification.

Methyl 7,8-dihydrofuro[*2,3-g*]indole-2-carboxylate, methyl 5,6-dihydrofuro[*3,2-f*]indole-2-carboxylate and methyl 5,6-dihydrofuro[*2,3-e*]indole-2-carboxylate

To stirred xylenes (800 mL) under Ar at reflux was added dropwise a solution of methyl 2-azido-3-(2,3-dihydrobenzo[*b*]furan-5-yl)propenate and methyl 2-azido-3-(2,3-dihydrobenzo[*b*]furan-7-yl)propenate (4:1 mixture; 11.4 g, 46.5 mmol) in xylenes (300 mL) over 3.5 h. After complete addition, the mixture was heated at reflux for a further 30 min, followed by removal of xylenes (750 mL) by distillation. The residual solution was allowed to cool, with stirring, to ambient temperature overnight.
The resultant precipitate was filtered and washed with cold xylenes to afford a mixture [(*2,3-g*):(*3,2-f*) - 1:1] of products (5.90 g, 59%) as a white solid which was used without further purification. The filtrate was concentrated *in vacuo* and the residue was recrystallised from hot xylenes (100 mL) to afford a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) - 12:48:40] of products (2.23 g, 22%) as a pale yellow solid.

7,8-Dihydrofuro[*2,3-g*]indole-2-carboxylic acid and 5,6-dihydrofuro[*3,2-f*]indole-2-carboxylic acid

To a stirred suspension of methyl 7,8-dihydrofuro[*2,3-g*]indole-2-carboxylate and methyl 5,6-dihydrofuro[*3,2-f*]indole-2-carboxylate (1:1) (5.85 g, 26.9 mmol) in water (140 mL) was added potassium hydroxide (85%; 3.55 g, 53.8 mmol) and the mixture was heated at reflux for 3.75 h, then allowed to cool to ambient temperature. Hydrochloric acid (2.5N aqueous; 29 mL) was added and the resultant precipitate was filtered and washed with water to afford a mixture [(*2,3-g*):(*3,2-f*) 1:1] of products (5.47 g, 100%) as an off-white solid which was used without further purification.

7,8-Dihydrofuro[*2,3-g*]indole and 5,6-dihydrofuro[*3,2-f*]indole

A stirred solution of 7,8-dihydrofuro[*2,3-g*]indole-2-carboxylic acid and 5,6-dihydrofuro[*3,2-f*]indole-2-carboxylic acid (1:1) (5.46 g, 26.9 mmol) in phenyl ether

(250 mL) was heated at reflux for 45 min, then allowed to cool to ambient temperature. Heptane (500 mL) was added and the mixture was passed through a heptane-packed SiO_2 column under pressure. The column was eluted with heptane (1.5 L), then heptane-dichloromethane (1:1, 1L) and finally dichloromethane to afford 7,8-dihydrofuro[*2,3-g*]indole (230 mg, 5.4%) as a white solid. IR ν_{max} (Nujol)/cm^{-1} 3382, 2925, 2854, 1644, 1618, 1497, 1463, 1441, 1435, 1368, 1326, 1234, 1140, 1021, 970, 793, 719, 622, 533 and 475; NMR (400 MHz, $CDCl_3$) δ_H 3.31 (2H, t, *J* 8.5 Hz), 4.66 (2H, t, *J* 8.5 Hz), 6.51 (1H, dd, *J* 2, 3.5 Hz), 6.73 (1H, d, *J* 8 Hz), 7.06 (1H, dd, *J* 2, 3.5 Hz), 7.39 (1H, d, *J* 8.5 Hz) and 7.83 (1H, brs). Also collected were 5,6-dihydrofuro[*3,2-f*]indole (667 mg, 15.6%) and mixed fractions (2.94 g, 68.7%). The mixed isomers were further separated by flash column chromatography [SiO_2; ethyl acetate-heptane (1:3)] to afford afford 7,8-dihydrofuro[*2,3-g*]indole (408 mg, 9.5%) as a white solid and 5,6-dihydrofuro[*3,2-f*]indole (690 mg, 16%).

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-7,8-dihydrofuro[*2,3-g*]indole

To a stirred solution of 7,8-dihydrofuro[*2,3-g*]indole (392 mg, 2.46 mmol) in dimethyl sulfoxide under Ar at 38 °C (external temperature) was added powdered potassium hydroxide (85%; 650 mg, 9.85 mmol) and the resultant suspension was stirred for 1 h. A solution of (*S*)-2-(tert-butoxycarbonylamino)propane methanesulfonate (1.50 g, 5.9 mmol) was added dropwise over 45 min, and the mixture was stirred for 4 days. After this time, the reaction was quenched by pouring onto ice-water (100 mL), the resultant suspension was filtered and the solid was washed with ice-cold water to afford the product (580 mg, 74%) as a pale pink solid. R_f 0.25 [Ethyl acetate-heptane (3:7)]; IR ν_{max} (Nujol)/cm^{-1} 3360, 2925, 2854, 1687, 1516, 1460, 1366, 1341, 1299, 1233, 1224, 1173, 1079, 969, 794, 712 and 608; NMR (400 MHz, $CDCl_3$) δ_H 1.09 (3H, d, *J* 6.5 Hz), 1.39 (9H, s), 3.52 (1H, m), 3.59 (1H, m), 3.99 (2H, m), 4.27 (1H, m), 4.63 (2H, t, *J* 9 Hz), 6.42 (1H, d, *J* 3.5 Hz), 6.68 (J, d, *J* 8.5 Hz), 6.89 (1H, d, *J* 3.5 Hz) and 7.33 (1H, d, *J* 8.5 Hz).

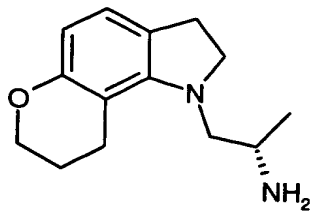
(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydrofuro[*2,3-g*]indole

To a stirred solution/suspension of (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-7,8-dihydrofuro[*2,3-g*]indole (565 mg, 1.79 mmol) in acetic acid (40 mL) under Ar at 5 °C was added sodium cyanoborohydride (371 mg, 5.90 mmol) and the mixture was allowed to warm to ambient temperature and stir overnight. The resultant solution was poured onto ice-water (100 mL), basified (~ pH 8-9) by the addition of 30% ammonium hydroxide, and the resultant suspension was filtered and the solid washed with ice-cold water. The crude solid was purified by flash column chromatography [SiO_2; ethyl acetate-heptane (3:7)] to afford the product (412 mg, 72%) as a white solid: mp 141-142.5 °C; Found: C, 67.87; H, 8.21; N, 8.80%. $C_{18}H_{26}N_2O_3$ requires: C, 67.90; H, 8.23; N, 8.79%.

(*S*)-1-(2,3,7,8-Tetrahydrofuro[*2,3-g*]indol-1-yl)-2-propylamine fumarate

To a stirred solution/suspension of (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-2,3,7,8-tetrahydrofuro[*2,3-g*]indole (392 mg, 1.23 mmol) in methanol (25 mL) was added conc. hydrochloric acid (0.37 mL) and the mixture was heated at reflux for 1.5 h, then allowed to cool to ambient temperature. The solvent was removed *in vacuo* and the residue was triturated with ether and a small amount of acetone, filtered, and washed with ether to afford the product (366 mg, 100%) as the bis-hydrochloride salt. 326 mg of this salt was partitioned between ether and aqueous sodium hydroxide solution, and the aqueous phase was extracted with ether. The combined organic fractions were dried (magnesium sulfate) and concentrated *in vacuo* to afford the free amine as a pale yellow oil (216 mg). A solution of the above oil in hot 2-propanol (0.5 mL) was added to a stirred solution of fumaric acid (127 mg, 1.09 mmol) in hot 2-propanol (2 mL), and the resultant suspension was allowed to cool to ambient temperature and was then cooled to 0 °C. The solid was filtered and washed with ice-cold 2-propanol, followed by ether to afford the product (279 mg, 76%) as a white solid: mp. 215.5-217 °C (dec.); Found: C, 60.98; H, 6.78; N, 8.26%. $C_{13}H_{18}N_2O.C_4H_4O_4$ requires: C, 61.07; H, 6.63; N, 8.37%.

Example 4: (*S*)-1-(2,3,7,8-Tetrahydro-*9H*-pyrano[*2,3-g*]indol-1-yl)-2-propylamine fumarate



Chroman

To a stirred solution of 4-hydroxychroman (10.14 g, 67.5 mmol) in acetic acid (150 mL) under Ar was added acetic anhydride (12.7 mL, 135 mmol) and the mixture was heated at reflux for 3 h, then allowed to cool to ambient temperature. Palladium on carbon (10wt%; 1.8 g, 2.5 mol%) was added and the mixture was shaken in a Parr hydrogenator under a 42 psi atmosphere of hydrogen overnight. The reaction mixture was filtered, the solvent was removed *in vacuo* and the residue was taken-up in ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate solution, brine, dried (magnesium sulfate) and concentrated *in vacuo* to afford the product (7.73 g, 85%) as a pale yellow liquid: IR ν_{max} (film)/cm^{-1} 2937, 2863, 1737, 1609, 1582, 1490, 1456, 1304, 1267, 1228, 1189, 1116, 1065, 1008 and 754; NMR (400 MHz, $CDCl_3$) δ_H 2.00 (2H, m), 2.78 (2H, t, *J* 6.5 Hz), 4.17 (2H, t, *J* 7 Hz), 6.81 (2H, m) and 7.05 (2H, m).

Chroman-6-carboxaldehyde and chroman-8-carboxaldehyde

A mixture of chroman-6-carboxaldehyde and chroman-8-carboxaldehyde was prepared according to the method described in Example 3, using chroman (7.70 g, 57.4 mmol) to produce a mixture [6-CHO : 8-CHO (1:1)] of aldehyde products (8.98 g, 96%) as a pale orange liquid which was used without further purification.

Methyl 2-azido-3-(2,3-dihydro-4*H*-benzopyran-6-yl)propenate and methyl 2-azido-3-(2,3-dihydro-4*H*-benzopyran-8-yl)propenate

Methyl 2-azido-3-(2,3-dihydro-4*H*-benzopyran-6-yl)propenate and methyl 2-azido-3-(2,3-dihydro-4*H*-benzopyran-8-yl)propenate were prepared according to the method

described in Example 3, using a mixture (1:1) of chroman-6-carboxaldehyde and chroman-8-carboxaldehyde (8.95 g, 55.2 mmol) to produce after purification by flash column chromatography [SiO_2; dichloromethane-heptane (1:1)] a mixture [6-substituted : 8-substituted (3:1)] of products (5.15 g, 36%) as a pale yellow solid which was used without further purification.

Methyl 7,8-dihydro-9*H*-pyrano[*2,3-g*]indole-2-carboxylate, methyl 6,7-dihydro-5*H*-pyrano[*3,2-f*]indole-2-carboxylate and methyl 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole-2-carboxylate

Methyl 7,8-dihydro-9*H*-pyrano[*2,3-g*]indole-2-carboxylate, methyl 6,7-dihydro-5*H*-pyrano[*3,2-f*]indole-2-carboxylate and methyl 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole-2-carboxylate were prepared according to the method described in Example 3, using a mixture (3:1) of methyl 2-azido-3-(2,3-dihydro-4*H*-benzopyran-6-yl)propenate and methyl 2-azido-3-(2,3-dihydro-4*H*-benzofuran-8-yl)propenate (5.1 g, 19.7 mmol) to produce a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) - 10:2:5] of products (4.33 g, 94%) as a yellow solid which was used without further purification.

7,8-Dihydro-9*H*-pyrano[*2,3-g*]indole-2-carboxylic acid, 6,7-dihydro-5*H*-pyrano[*3,2-f*]indole-2-carboxylic acid and 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole-2-carboxylic acid

7,8-Dihydro-9*H*-pyrano[*2,3-g*]indole-2-carboxylic acid, 6,7-dihydro-5*H*-pyrano[*3,2-f*]indole-2-carboxylic acid and 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole-2-carboxylic acid were prepared according to the method described in Example 3, using a mixture (10:5:2) of methyl 7,8-dihydro-9*H*-pyrano[*2,3-g*]indole-2-carboxylate, methyl 6,7-dihydro-5*H*-pyrano[*3,2-f*]indole-2-carboxylate and methyl 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole-2-carboxylate (4.33 g, 18.7 mmol) to produce, after trituration with isopropyl ether, a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) - 7:1:2] of products (2.30 g, 57%) as a white solid. The filtrate was evaporated and purified by flash column chromatography [SiO_2; ethyl acetate-heptane (2:1) + 0.5% acetic acid] to afford an oil which solidified upon treatment with isopropyl ether-heptane to afford a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) - 44:22:34] of products (818 mg, 20%) as a white solid. The products were combined and used without further purification.

7,8-Dihydro-9*H*-pyrano[*2,3-g*]indole, 6,7-dihydro-5*H*-pyrano[*3,2-g*]indole and 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole

7,8-Dihydro-9*H*-pyrano[*2,3-g*]indole, 6,7-dihydro-5*H*-pyrano[*3,2-g*]indole and 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole were prepared according to the procedure described in Example 3, using a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) - 11:1:4] of 7,8-dihydro-9*H*-pyrano[*2,3-g*]indole-2-carboxylic acid, 6,7-dihydro-5*H*-pyrano[*3,2-f*]indole-2-carboxylic acid and 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole-2-carboxylic acid (3.12 g, 14.4 mmol) to produce, after flash column chromatography (and without further separation on a second column) a mixture [(*2,3-g*):(*2,3-e*) – 72:28] of products (2.01 g, 80%) as a white, crystalline solid [R_f 0.46 (SiO_2; dichloromethane)] which was used without further purification. Also collected was 6,7-dihydro-*5H*-pyrano[3,2-f]indole (250 mg, 10%) as an off-white solid [R_f 0.33 (SiO_2; dichloromethane)].

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-7,8-dihydro-9*H*-pyrano[*2,3-g*]indole

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-7,8-dihydro-9*H*-pyrano[*2,3-g*]indole was prepared according to the method described in Example 3, using a mixture [(*2,3-g*):(*2,3-e*) - 7:3] of 7,8-dihydro-9*H*-pyrano[*2,3-g*]indole and 5,6-dihydro-7*H*-pyrano[*2,3-e*]indole (1.34 g, 7.7 mmol) to produce, after purification by flash column chromatography [SiO_2; ethyl acetate-heptane (1:4)], the product (890 mg, 35%) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 3352, 2925, 2855, 1687, 1611, 1528, 1458, 1424, 1367, 1358, 1247, 1167, 1054, 961, 704 and 632; NMR (400 MHz, $CDCl_3$) δ_H 1.03 (3H, d, *J* 7 Hz), 1.36 (9H, s), 3.10 (1H, m), 3.18 (1H, m), 3.94 (1H, sept, *J* 7 Hz), 4.12 (1H, m), 4.15 (2H, dd, *J* 4.5, 6 Hz), 4.46 (1H, m), 6.35 (1H, d, *J* 3 Hz), 6.63 (1H, d, *J* 8.5 Hz), 6.82 (1H, d, *J* 3 Hz) and 7.27 (1H, d, *J* 8.5 Hz).

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydro-9*H*-pyrano[*2,3-g*]indole

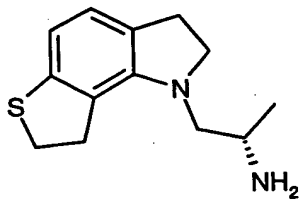
(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydro-9*H*-pyrano[*2,3-g*]indole was prepared according to the procedure described in Example 3, using (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-7,8-dihydro-9*H*-pyrano[*2,3-g*]indole (870 mg, 2.63

mmol) with the following modification. After the basification step, the mixture was extracted with chloroform, washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to afford the product (860 mg, 98%) as a white solid: mp. 137-140 °C; Found: C, 68.71; H, 8.49; N, 8.39%. $C_{19}H_{28}N_2O_3$ requires: C, 68.65; H, 8.49; N, 8.42%.

(*S*)-1-(2,3,7,8-Tetrahydro-9*H*-pyrano[2,3-*g*]indol-1-yl)-2-propylamine fumarate

(*S*)-1-(2,3,7,8-Tetrahydro-9*H*-pyrano[2,3-*g*]indol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 3, using (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-2,3,7,8-tetrahydro-9*H*-pyrano[2,3-*g*]indole (820 mg, 2.47 mmol) with the following modification. After evaporation of the methanol, the residue was partitioned between ether and aqueous sodium hydroxide (2N), the aqueous phase was extracted with ether, dried (magnesium sulfate) and concentrated *in vacuo* to afford the free amine as a pale yellow oil (572 mg, 100%). The fumarate was formed according to the procedure described in Example 3, giving the product (728 mg, 79%) as a white solid: mp. 168-169 °C; Found: C, 62.02; H, 7.14; N, 8.02%. $C_{14}H_{20}N_2O.C_4H_4O_4$ requires: C, 62.05; H, 6.94; N, 8.04%.

Example 5: (*S*)-1-(2,3,7,8-Tetrahydrothieno[2,3-*g*]indol-1-yl)-2-propylamine fumarate



2,3-Dihydrobenzo[*b*]thiophene, 1,1-dioxide

To a stirred solution/suspension of benzo[*b*]thiophene, 1,1-dioxide (25.0 g, 0.15 mol) in a mixture of tetrahydrofuran (165 mL) and ethanol (110 mL) under Ar at ambient temperature was added palladium on carbon (10wt%; 880 mg) and the mixture was shaken under a 20 psi hydrogen atmosphere for 15 min. The reaction mixture was filtered and concentrated *in vacuo* to afford the product (24.68 g, 98%) as a yellow oil:

IR ν_{max} (Nujol)/cm^{-1} 2925, 2854, 1600, 1456, 1378, 1292, 1266, 1196, 1148, 1120, 1060, 982, 854, 787, 746, 600, 549 and 516; NMR (400 MHz, $CDCl_3$) δ_H 3.35 (2H, t, *J* 6.5 Hz), 3.68 (2H, t, *J* 6.5 Hz), 7.52 (1H, m), 7.55 (1H, m), 7.66 (1H, dt, *J* 7.5, 1 Hz), 7.74 (1H, d, *J* 7.5 Hz).

2,3-Dihydrobenzo[*b*]thiophene

To a stirred solution of 2,3-dihydrobenzo[*b*]thiophene, 1,1-dioxide (24.62 g, 146 mmol) in tetrahydrofuran (350 mL) under Ar at ambient temperature was added a solution of lithium aluminium hydride (1.0 M in tetrahydrofuran; 161 mL, 161 mmol) dropwise over 10 min, then the mixture was heated at reflux for 30 min. The reaction was allowed to cool to ambient temperature, then quenched by the dropwise addition of water (6.6 mL) followed by 15% aqueous sodium hydroxide (6.6 mL), then water (19.9 mL). The mixture was filtered, diluted with ether, washed with brine, dried (magnesium sulfate) and concentrated *in vacuo* to afford the crude product. Purification by flash column chromatography (SiO_2; heptane) afforded the product (4.80 g, 24%) as a pale yellow oil: R_f 0.35 (heptane); NMR (400 MHz, $CDCl_3$) δ_H 3.27 (1H, m), 3.28 (1H, d, *J* 7 Hz), 3.33 (1H, d, J *7* Hz), 3.35 (1H, dd, *J* 2.5, 4 Hz), 7.00 (1H, dt, *J* 1.5, 6 Hz), 7.10 (1H, dt, *J* 1.5, 6 Hz), 7.18 (1H, d, *J* 7.5 Hz), 7.21 (1H, d, *J* 7.5 Hz).

2,3-Dihydrobenzo[*b*]thiophene-5-carboxaldehyde and 2,3-Dihydrobenzo[*b*]thiophene-7-carboxaldehyde

A mixture of 2,3-dihydrobenzo[*b*]thiophene-5-carboxaldehyde and 2,3-dihydrobenzo[*b*]thiophene-7-carboxaldehyde was prepared according to the method described in Example 3, using 2,3-dihydrobenzo[*b*]thiophene (4.8 g, 35.2 mmol) to produce, after purification by flash column chromatography [SiO_2; heptane-ether (4:1 → 2:1)] a mixture [5-CHO : 7-CHO (1.3:1)] of aldehyde products (2.55 g, 44%) as a yellow oil which was used without further purification.

Methyl 2-azido-3-(2,3-dihydrobenzo[*b*]thiophene-5-yl)propenate and methyl 2-azido-3-(2,3-dihydrobenzo[*b*]thiophene-7-yl)propenate

Methyl 2-azido-3-(2,3-dihydrobenzo[*b*]thiophene-5-yl)propenate and methyl 2-azido-3-(2,3-dihydrobenzo[*b*]thiophene-7-yl)propenate were prepared according to the method described in Example 3, using the above mixture (1.3:1) of 2,3-dihydrobenzo[*b*]thiophene carboxaldehydes and (2.55 g, 15.53 mmol) to produce (without purification by flash column chromatography) a mixture [5-substituted : 7-substituted (1.4:1)] of products (3.61 g, 89%) as a pale yellow oil which was used without further purification.

Methyl 7,8-dihydrothieno[*2,3-g*]indole-2-carboxylate, methyl 5,6-dihydrothieno[*3,2-f*]indole-2-carboxylate and methyl 5,6-dihydrothieno[*2,3-e*]indole-2-carboxylate

Methyl 7,8-dihydrothieno[*2,3-g*]indole-2-carboxylate, methyl 5,6-dihydrothieno[*3,2-f*]indole-2-carboxylate and methyl 5,6-dihydrothieno[*2,3-e*]indole-2-carboxylate were prepared according to the method described in Example 3, using a mixture (1.4:1) of the above 2-azidopropenates (3.61 g, 13.8 mmol), with the following modification. The addition of the substrate to the refluxing xylenes was carried out over 2.5 h, heated for a further 0.5 h, then allowed to cool to ambient temperature. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; dichloromethane) to afford a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) – 34:44:22] of products (1.92 g, 60%) as a white solid which was used without further purification.

7,8-dihydrothieno[*2,3-g*]indole-2-carboxylic acid, 5,6-dihydrothieno[*3,2-f*]indole-2-carboxylic acid and 5,6-dihydrothieno[*2,3-e*]indole-2-carboxylic acid

7,8-dihydrothieno[*2,3-g*]indole-2-carboxylic acid, 5,6-dihydrothieno[*3,2-f*]indole-2-carboxylic acid and 5,6-dihydrothieno[*2,3-e*]indole-2-carboxylic acid were prepared according to the method described in Example 3, using a mixture (34:44:22) of the above methyl dihydrothienoindole-2-carboxylates (1.84 g, 7.89 mmol) to produce a mixture [(*2,3-g*):(*3,2-f*):(*2,3-e*) - 41:35:24] of products (1.65 g, 95%) as a pale green solid which was used without further purification.

7,8-Dihydrothieno[*2,3-g*]indole, 5,6-dihydrothieno[*3,2-f*] and 5,6-dihydrothieno[*2,3-e*]indole

7,8-Dihydrothieno[*2,3-g*]indole, 5,6-dihydrothieno[*3,2-f*] and 5,6-dihydrothieno[*2,3-e*]indole were prepared according to the method described in Example 3, using the above mixture of dihydrothienoindole-2-carboxylic acids (1.64 g, 7.48 mmol), with the following modification. After the mixture had been passed down the heptane-packed column and the phenyl ether flushed-off with heptane, the eluant was increased to heptane-dichloromethane (1:1 → 1:3) to afford a purple solid. The solid was recrystallised [heptane-isopropyl ether (1:1)] to afford a mixture (2:3) of 7,8-dihydrothieno[*2,3-g*]indole and 5,6-dihydrothieno[*3,2-f*]indole (540 mg, 41%) as a pink solid. The filtrate was evaporated to afford a mixture (25:30:45) of 7,8-dihydrothieno[*2,3-g*]indole, 5,6-dihydrothieno[*3,2-f*]indole and 5,6-dihydrothieno[*2,3-e*]indole (644 mg, 49%) as a purple solid which was used without further purification.

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-7,8-dihydrothieno[*2,3-g*]indole

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-7,8-dihydrothieno[*2,3-g*]indole was prepared according to the method described in Example 3, using a mixture (25:30:45) of 7,8-dihydrothieno[*2,3-g*]indole, 5,6-dihydrothieno[*3,2-f*]indole and 5,6-dihydrothieno[*2,3-e*]indole (617 mg, 3.52 mmol) to afford, after purification by flash column chromatography [SiO_2; ethyl acetate-heptane (1:3)], the product (200 mg, 17%) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 3347, 2922, 2855, 1680, 1520, 1460, 1378, 1364, 1314, 1252, 1169, 1056, 884, 798 and 721; NMR (400 MHz, $CDCl_3$) δ_H 1.08 (3H, d, *J* 7 Hz), 1.40 (9H, s), 3.45 (2H, dt, *J*, 1.5, 6 Hz), 3.61 (1H, m), 3.72 (1H, m), 3.98 (1H, m), 4.08 (1H, m), 4.39 (2H, m), 6.42 (1H, d, *J* 3 Hz), 6.90 (1H, d, *J* 3Hz), 6.98 (1H, d, *J* 8 Hz), 7.38 (1H, d, *J* 8 Hz).

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydrothieno[*2,3-g*]indole

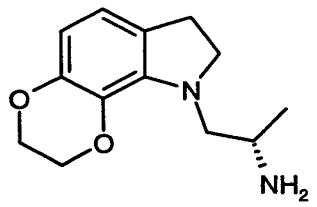
(*S*)-1-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydrothieno[*2,3-g*]indole was prepared according to the method described in Example 3, using (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-7,8-dihydrothieno[*2,3-g*]indole (200 mg, 0.60 mmol) to

produce, after purification by flash column chromatography [SiO_2; ethyl acetate-heptane (1:4)], the product (138 mg, 69%) as a pale green solid: mp. 170-171.5 °C; Found: C, 64.60; H, 7.72; N, 8.37%. $C_{18}H_{26}N_2O_2S$ requires: C, 64.64; H, 7.83; N, 8.37%.

(*S*)-1-(2,3,7,8-Tetrahydrothieno[*2,3-g*]indol-1-yl)-2-propylamine fumarate

(*S*)-1-(2,3,7,8-Tetrahydrothieno[*2,3-g*]indol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 3, using (*S*)-1-[2-(*tert*-butoxycarbonylamino)propyl]-2,3,7,8-tetrahydrothieno[*2,3-g*]indole (122 mg, 0.36 mmol) to produce the product (104 mg, 82%) as a white solid: mp. 188-189.5 °C (dec.); Found: C, 57.98; H, 6.33; N, 7.90%. $C_{13}H_{18}N_2S.C_4H_4O_4$ requires: C, 58.27; H, 6.33; N, 7.99%.

Example 6: (*S*)-1-(2,3,7,8-Tetrahydro-*9H*-1,4-dioxino[*2,3-g*]indol-9-yl)-2-propylamine fumarate



Methyl 2-azido-3-(1,4-benzodioxan-6-yl)propenate

Methyl 2-azido-3-(1,4-benzodioxan-6-yl)propenate was prepared according to the method described in Example 3, using 1,2-benzodioxan-6-carboxaldehyde (4.67 g, 28.5 mmol) to produce the product (3.89 g, 52%) as a pale yellow solid: IR ν_{max} (Nujol)/cm^{-1} 2925, 2854, 2121, 1710, 1699, 1620, 1608, 1601, 1576, 1508, 1466, 1434, 1381, 1317, 1300, 1265, 1252, 1236, 1211, 1165, 1157, 1125, 1084, 1066, 1050, 967, 952, 920, 906, 888, 862, 840, 805, 774, 756, 725, 663, 616 and 563; NMR δ_H (400 MHz; $CDCl_3$) 3.39

(1H, s), 4.25-4.31 (4H, m), 6.81 (1H, s), 6.86 (1H, d, *J* 8.5 Hz), 7.24 (1H, dd, *J* 8.5, 2.0 Hz) and 7.51 (1H, d, *J* 2.0 Hz).

Methyl 2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole-8-carboxylate

Methyl 2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole-8-carboxylate was prepared according to the procedure described in Example 3, using methyl 2-azido-3-(1,4-benzodioxan-6-yl)propenate (3.81 g, 14.58 mmol), with the following modification. The addition of the substrate to the refluxing xylenes was carried out over 5 h, the mixture was heated for a further 0.5 h, then the solvent was removed *in vacuo*. The resultant crude product was purified by flash column chromatography (SiO_2; dichloromethane) to afford the product (1.58 g, 46%) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 3302, 2927, 2855, 1748, 1712, 1694, 1634, 1589, 1548, 1513, 1455, 1392, 1377, 1320, 1277, 1257, 1200, 1102, 1084, 1019, 990, 935, 910, 875, 835, 824, 802, 788, 773, 748, 742, 685, 634, 596, 583, 562, 546, 534, 486 and 458; NMR δ_H (400 MHz; $CDCl_3$) 3.92 (1H, s), 4.32-4.39 (4H, m), 6.75 (1H, d, J 8.5 Hz), 7.11-7.15 (2H, m) and 8.90 (1H, br s).

2,3-Dihydro-9*H*-1,4-dioxino[*2,3-g*]indole-8-carboxylic acid

2,3-Dihydro-9*H*-1,4-dioxino[*2,3-g*]indole-8-carboxylic acid was prepared according to the method described in Example 3, using methyl 2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole-8-carboxylate (1.61 g, 6.90 mmol) to produce, after recrystallisation [ethanol-water (1:2)], the product (1.25 g, 82%) as a pale pink crystalline solid: mp 222-223 °C (dec.); Found: C, 60.06; H, 4.11; N, 6.33%. $C_{11}H_9NO_4$ requires: C, 60.28; H, 4.14; N, 6.39%.

2,3-Dihydro-9*H*-1,4-dioxino[*2,3-g*]indole

2,3-Dihydro-9*H*-1,4-dioxino[*2,3-g*]indole was produced according to the method described in Example 3, using 2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole-8-carboxylic acid (1.192 g, 5.44 mmol) to produce the product (934 mg, 98%) as a pale yellow oil: NMR δ_H (400 MHz; $CDCl_3$) 4.27-4.37 (4H, m), 6.65 (1H, d, J 8.5 Hz), 7.01 (1H, d, J

2.0 Hz), 7.07 (1H, d, J 8.5 Hz), 11.52 (1H, s) and 12.65 (1H, br s); Found: C, 68.56; H, 5.12; N, 7.75%. $C_{10}H_9NO_2$ requires: C, 68.56; H, 5.18; N, 7.99%.

(*S*)-9-[2-(*tert*-Butoxycarbonylamino)propyl]-(2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole

(*S*)-9-[2-(*tert*-Butoxycarbonylamino)propyl]-(2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole was prepared according to the procedure described in Example 3, using 2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole (875 mg, 4.99 mmol) to produce, after purification by flash column chromatography [SiO_2; ethyl acetate-heptane (1:4 → 3:7)], the product (1.113 g, 67%) as a white solid: IR ν_{max} (Nujol)/cm^{-1} 3420, 3104, 2926, 2825, 1705, 1627, 1583, 1506, 1460, 1434, 1376, 1367, 1352, 1322, 1272, 1257, 1205, 1178, 1160, 1090, 1059, 966, 878, 795, 714, 632 and 492; NMR (400 MHz, $CDCl_3$) δ_H 1.11 (3H, d, *J* 6.5 Hz), 1.28 (9H, s), 4.00 (1H, sept, *J* 7 Hz), 4.21 (1H, m), 4.30 (2H, dt, *J* 1,3.5 Hz), 4.36 (2H, dt, *J* 3.5, 1 Hz), 4.74 (1H, m), 6.35 (1H, d, *J* 3 Hz), 6.65 (1H, d, *J* 8.5 Hz), 6.86 (1H, d, *J* 3 Hz), 7.01 (1H, d, *J* 8.5 Hz).

(*S*)-9-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydro-9*H*-1,4-dioxino[*2,3-g*]indole

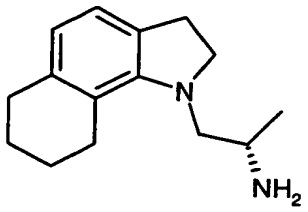
(*S*)-9-[2-(*tert*-Butoxycarbonylamino)propyl]-2,3,7,8-tetrahydro-9*H*-1,4-dioxino[*2,3-g*]indole was prepared according to the procedure described in Example 3, using (*S*)-9-[2-(*tert*-butoxycarbonylamino)propyl]-(2,3-dihydro-9*H*-1,4-dioxino[*2,3-g*]indole (1.09 g, 3.28 mmol) to produce, after purification by flash column chromatography [SiO_2; ethyl acetate-heptane (1:4)], the product (896 mg, 81%) as a white solid: mp 129.5-132 °C; Found: C, 64.61; H, 7.87; N, 8.32%. $C_{18}H_{26}N_2O_4$ requires: C, 64.65; H, 7.84; N, 8.37%

(*S*)-1-(2,3,7,8-Tetrahydro-9*H*-1,4-dioxino[*2,3-g*]indol-9-yl)-2-propylamine fumarate

(*S*)-1-(2,3,7,8-Tetrahydro-9*H*-1,4-dioxino[*2,3-g*]indol-9-yl)-2-propylamine fumarate

was prepared according to the procedure described in Example 3, using (*S*)-9-[2-(*tert*-butoxycarbonylamino)propyl]-2,3,7,8-tetrahydro-9*H*-1,4-dioxino[*2,3-g*]indole (870 mg, 2.60 mmol) to produce the product (723 mg, 79%) as a white solid: mp 173-174 °C (dec.); Found: C, 58.09; H, 6.36; N, 7.95%. $C_{13}H_{18}N_2O_2.C_4H_4O_4$ requires: C, 58.28; H, 6.33; N, 7.99%

Example 7: (*S*)-1-(2,3,6,7,8,9-Hexahydro-1*H*-benz[*g*]indol-1-yl)]-2-propylamine, fumarate



6,7,8,9-Tetrahydro-1*H*-benz[*g*]indole-2,3-dione

The benz[*g*]isatin was prepared in two steps from 5,6,7,8-tetrahydro-1-naphthylamine using the methods described for 1,6,7,8-tetrahydrocyclopenta[g]indole-2,3-dione (G. W. Rewcastle et. al., *J. Med. Chem.*, 1991, **34**, 217). The product (54% yield from N-[1-(5,6,7,8-tetrahydronaphthalenyl)]-2-(hydroximino)acetamide) was obtained as an orange solid: mp. 234-235 °C (lit. [US 1856210, 1929] 232 °C); NMR δ_H (400 MHz; DMSO-d_6) 1.73 (4H, m), 2.49 (2H, m), 2.73 (2H, m), 6.78 (1H, d, *J* 7.7 Hz), 7.21 (1H, d, *J* 7.7 Hz) and 10.92 (1H, s).

6,7,8,9-Tetrahydro-1*H*-benz[*g*]indole

To a suspension of lithium aluminium hydride (2.85 g, 75.0 mmol) in dry tetrahydrofuran (150 mL) was added 6,7,8,9-tetrahydro-1*H*-benz[g]indole-2,3-dione (3.018 g, 15.0 mmol) portionwise over 30 min. The green suspension was heated under reflux for 18 h and then cooled to 0 °C. The suspension was treated with water (2.8

mL), 5 N aqueous sodium hydroxide (2.1 mL), and water (9.2 mL), and was stirred for an additional 1 h. The suspension was then filtered, the residue was washed with tetrahydrofuran. and the filtrate then concentrated *in vacuo*. The residue obtained was purified by column chromatography [SiO_2; ethyl acetate-heptane (1:19)] and triturated with hexane to give the title indole (1.58 g, 62%) as a white solid: mp. 93-94 °C (lit. [*Khim. Geterotsikl. Soedin.*, 1978, **14**, 634] 89-90 °C); Found: C, 84.25; H, 7.65; N, 8.16%. $C_{12}H_{13}N$ requires C, 84.17; H, 7.65; N, 8.18%.

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)]-6,7,8,9-tetrahydro-1*H*-benz[*g*]indole

To a suspension of powdered potassium hydroxide (85%; 2.11 g, 32.0 mmol) in methyl sulfoxide (30 mL) at 40 °C was added 6,7,8,9-tetrahydro-1*H*-benz[*g*]indole (1.37 g, 8.0 mmol). The green suspension was stirred at 40 °C for 1 h, and then a solution of (*S*)-2-(*tert*-butoxycarbonylamino)propane methanesulfonate (5.07 g, 20.0 mmol) in methyl sulfoxide (10 mL) was added dropwise over 1 h. The suspension was heated at 40 °C for 66 h, poured onto a mixture of ice (150 g) and water (50 mL) and extracted with isopropyl ether (2 x 50 mL). The combined organic extracts were washed with water (50 mL), dried (sodium sulfate) and concentrated *in vacuo*. The residue obtained was purified by column chromatography [SiO_2; ethyl acetate-heptane (1:1)] and triturated with hexane to give the title carbamate (1.49 g, 57%), as a white solid: mp. 118-119 °C; Found: C, 72.65; H, 8.75; N, 8.45%. $C_{20}H_{28}N_2O_2$ requires C, 73.14; H, 8.59; N, 8.52%; NMR δ_H (400 MHz; CDCl3) 7.34 (1 H, d, *J* 8.0 Hz), 6.92 (1 H, m), 6.82 (1 H, d, *J* 8.0 Hz), 6.40 (1 H, m), 4.4 (1 H, br), 4.28 (1 H, m, *J* 6.5 Hz), 3.96 (1 H, m, *J* 6.8 Hz), 3.16 (2 H, m), 2.91 (2 H, m), 1.89 (2 H, m), 1.83 (2 H, m), 1.45 (9 H, br s) and 1.07 (3 H, d, *J* 6.8 Hz).

(*S*)-1-[2-(*tert*-Butoxycarbonylamino)]-2,3,6,7,8,9-hexahydro-1*H*-benz[*g*]indole

To a solution of (*S*)-1-[2-(*tert*-butoxycarbonylamino)]-6,7,8,9-tetrahydro-1*H*-benz[*g*]indole (0.985 g, 3.0 mmol) in acetic acid (50 mL) cooled in ice was added sodium cyanoborohydride (0.60 g, 9.55 mmol) in one portion. The solution was stirred for 18 h and was poured onto a mixture of ice (150 g) and water (50 mL). The suspension was stirred for 15 min and more ice was added. The suspension was basified

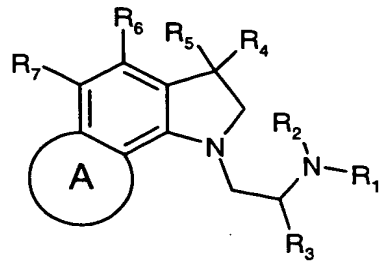
with ammonium hydroxide (140 mL) and extracted with ethyl acetate (2 x100 mL). The combined organic extracts were washed with water (100 mL), dried (magnesium sulfate) and concentrated *in vacuo*. The residue obtained was purified by column chromatography [SiO_2; ethyl acetate:heptane (1:4)] to give the title carbamate (0.935 g, 94%) as a pale purple solid: mp. 91-91.5 °C; Found: C, 72.7; H, 9.2; N, 8.4 %. $C_{20}H_{30}N_2O_2$ requires C, 72.7; H, 9.15; N, 8.5%; NMR (400 MHz, $CDCl_3$) δ_H 6.90 (1 H, d, *J* 7.5 Hz), 6.58 (1 H, d, *J* 7.5 Hz), 4.69 (1 H, br s), 3.84 (1 H, m), 3.42 (2 H, m), 3.14 (1 H, m), 2.99 (3 H, m), 2.77 (2 H, m), 2.66 (2 H, m), 1.75 (4 H, m), 1.44 (9 H, s) and 1.26 (3 H, d, *J* 6.6 Hz).

(*S*)-1-(2,3,6,7,8,9-Hexahydro-1*H*-benz[*g*]indol-1-yl)]-2-propylamine fumarate

To a stirred solution of (*S*)-1-[2-(*tert*-butoxycarbonylamino)]-2,3,6,7,8,9-hexahydro-1*H*-benz[*g*]indole (0.859 g, 2.60 mmol) in methanol (8.6 mL) was added hydrogen chloride (4 M in dioxan; 6.5 mL, 26 mmol). The solution was stirred for 3 h and was concentrated *in vacuo*. The oil was partitioned between dichloromethane (25 mL) and 0.5 N aqueous sodium hydroxide (25 mL), and the aqueous phase was extracted with dichloromethane (25 mL). The combined organic phases were washed with water (25 mL), dried (sodium sulfate) and concentrated *in vacuo* to give an oil which was dissolved in 2-propanol (7 mL) at 40 °C. The solution was added dropwise to a solution of fumaric acid (0.377 g, 3.25 mmol) in 2-propanol (7 mL) at 0 °C. The white suspension was cooled to 0 °C and filtered. The filter-cake was washed with 2-propanol and ether and dried to give the title compound (0.789 g, 79%) as a white solid: mp. 178-182 °C; Found: C, 65.6; H, 7.6; N, 8.05 %. $C_{15}H_{22}N_2.C_4H_4O_4$ requires C, 65.9; H, 7.6; N, 8.1%; NMR (400 MHz; DMSO-d_6) δ_H 6.84 (1 H, d, *J* 7.5 Hz), 6.52 (1 H, d, *J* 7.5 Hz), 6.44 (2 H, s), 3.37 (2 H, m), 3.23 (2 H, m), 3.00 (1 H, m), 2.89 (2 H, m), 2.64 (4 H, m), 1.65 (4 H, m) and 1.26 (3 H, d, *J* 6.5 Hz).

CLAIMS

1. A chemical compound of formula (I):



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen and alkyl;

R_3 is alkyl;

R_4 and R_5 are selected from hydrogen and alkyl;

R_6 and R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl, nitro, carbonitrile, carbo-alkoxy, carbo-aryloxy and carboxyl;

A is an optionally substituted 5 or 6-membered unsaturated or saturated ring optionally containing one or more heteroatoms.

2. A compound according to claim 1 wherein R_1 is the same as R_2.

3. A compound according to claim 1 wherein R_1 and R_2 are hydrogen.

4. A compound according to claim 1, 2 or 3 wherein R_3 is loweralkyl.

5. A compound according to claim 1, 2 or 3 wherein R_3 is methyl.

6. A compound according to any of claims 1 to 5 wherein one or more of R_4 to R_7 is/are hydrogen.

7. A compound according to any one of claims 1 to 6 wherein A is a 5 or 6 membered ring containing one heteroatom.

8. A compound according to claim 1 wherein the compounds of formula (I) are selected from (*S*)-1-(benz[*g*]indolin-1-yl)-2-propylamine fumarate, (*S*)-2-(2,3,7,8-tetrahydro-1*H*-furo[2,3-*g*]indol-1-yl)-2-propylamine fumarate, (*S*)-2-(2,3,7,8-tetrahydro-1*H*-thieno[2,3-*g*]indol-1-yl)-2-propylamine fumarate and (*S*)-2-(2,3,7,8-tetrahydro-7*H*-pyrano[2,3-*g*]indol-1-yl)-2-propylamine fumarate.

9. A compound of formula (I) as set out in any one of claims 1 to 8 for use in therapy.

10. The use of a compound of formula (I) as set out in any of claims 1 to 8 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

11. A use according to claim 10 wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

12. A use according to claim 10 wherein the damage to the central nervous system is by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases.

13. A use according to claim 12 wherein said toxic or infective CNS disease is encephalitis or meningitis.

14. A use according to claim 10 wherein the cardiovascular disorder is thrombosis.

15. A use according to claim 10 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility

16. A use according to claim 10 wherein said medicament is for the treatment of obesity.

17. A use according to any one of claims 10 to 16 wherein said treatment is prophylactic treatment.

18. A method of treatment of any of the disorders set out in claims 10 to 15 comprising administering to a patient in need of such treatment an effective dose of a compound of formula (I) as set out in any one of claims 1 to 8.

19. A method of treatment according to claim 18 wherein said disorder is obesity.

20. A method according to claim 18 or 19 wherein said treatment is prophylactic treatment..

21. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 8.

22. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 8 in combination with a pharmaceutically acceptable carrier or excipient.

23. A method of making a composition according to claim 22 comprising combining a compound of formula (I) as set out in any one of claims 1 to 8 with a pharmaceutically acceptable carrier or excipient.